REMARKS

Claims 1-18 currently are pending. Claim 7-18 have been withdrawn from consideration. Claims 1,and 3-5 have been amended. Claim 6 is allowed.

Specification

The statement at page 13, lines 30-32 has been deleted.

35 USC § 112, second paragraph

Applicants amend the claims to recite "selected from the group consisting of" instead of "selected from the group."

The Examiner stated that claim 1 is confusing in the lack of teachings in the specification as to how the random mutagenesis is controlled such as the picking and choosing is made.

In response, applicants point out that breadth of a claim is not to be equated with indefiniteness. *In re Miller,* 441 F.2d 689, 169 USPQ 597 (CCPA 1971). It is acknowledged that the variability of X^1-X^6 makes claim 1 broad. However, a person of ordinary skill in art would be able to determine the metes and bounds of claim 1 because the peptide fragments sequence would be definitely determined even though variables X^1-X^6 maybe, at least in part, co-dependent. This is not entirely relevant to "how the random mutagenesis is controlled such as the picking and choosing is made."

The Examiner stated that claim 2 is indefinite as to which definition of X^1-X^2 is being referenced to by the language "have the meanings stated in claim 1" since there are six different meanings in the base claim for X^1-X^6. Again, applicants remind the Examiner that breadth of a claim is not to be equated with indefiniteness. *In re Miller,*

441 F.2d 689, 169 USPQ 597 (CCPA 1971). There are different meanings in the base claim for X^1-X^6. However, this does not make the scope of the subject matter embraced by the claims unclear.

35 USC § 103

The Examiner rejected claims 1-4 under 35 USC § 103(a) as being unpatentable over Volz et al. and Guerinot et al. because the Examiner believes it would have been obvious to one of ordinary skill in the art at the time the invention was made to replace Leu in the peptide fragment of Volz with a homologous amino acid, Ile with reasonable expectation that the binding property of the peptide fragment of Volz is maintained since Guerinot teaches that these residues are conservatively substituted with one another.

Applicants traverse the Examiner's obviousness rejection because applicants believe the motivation to combine Volz et al., Haymore et al. and Guerinot et al. has not been established adequately by the Examiner.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Also, a statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made;" because the references relied upon teach that all aspects

of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reasons to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

Volz et al. teach the characterization of the metal-binding domain of the ATPase-439 and ATPase-948 of *Helicobacter pylori* (Abstract and page 29, last paragraph). It was possible for Volz et al. to purify said ATPases without using an additional His-tag sequence (see page 29, Abstract, last sentence and page 37, conclusions, last sentence.) Volz et al. do not teach anything about a method using the motif HxHxxxCxxC for the purification of other proteins or fusion proteins between said motif and other protein. Since Volz et al. do not discuss a general method of using parts of the ATPase or the motif for the purification of proteins applicants do not see why the skilled worker would use part of the ATPase of the motif for the purification of proteins.

In addition, applicants' own studies have shown that these ATPase binding sites display a binding affinity which is too low for efficient purification of all desired proteins (specification page 2, lines 40 to 45). Applicants' sequences bind to immobilized metal ions at least 1.5 times more strongly than the *Helicobacter pylori* ATPase-439 (page 9, lines 28-32 and page 14, lines 39-46) and are therefore useful for the purification of a lot of proteins. By using the advantageous sequences, it is possible to purify proteins in a very high yield (page 14, lines 43 to 46). Nothing is mentioned about this in Volz et al. Therefore, applicants do not see why the skilled worker should consider Volz et al.

Guerinot et al. teach the discovery of a family of polypeptide, designated as metal-regulated transporter, MRP, polypeptide, which share several structural/functional properties, at least one of which is related to metal transport (see column 2, lines 24-28, claims 23 and 24). Functionally, the MRT polypeptide are capable of, for example, transporting metals, e.g., Fe, Fe(II), Cd, Co, Mn, Pb, Hg and/or Zn (see col. 2, lines 35-37).

The MRT proteins disclosed by Guerinot et al. have four histidine rich domains (see col. 2, line 44). In Fig. 1A such a histidine rich domain is disclosed. It has the following sequence: His-Gly-His-Gly-His-Gly-His-Gly-. This protein fragment is totally different from the claimed protein fragments.

Also, the disclosure mentioned by the Examiner in Guerinot et al. col. 14, line 27 is a general teaching that the amino acids Ile and Leu belong to the group of amino acids which have uncharged side chains and therefore a skilled worker would change the codon usage of a given nucleic acid sequence coding for example for Leu to the codon usage of Ile in the event he is interested in mutagenizing the said sequence without changing the activity of the enzyme encoded by the sequence. These types of changes are only possible as disclosed by Guerinot et al. in areas which are not essential for the activity of the MRP proteins (see col. 14, lines 30 to 33).

Haymore et al. teach different proteins for immobilized-metal affinity chromatography. None of the disclosed proteins (see page 4, table, lines 15 to 33) share any homology with applicants' inventive sequences. The sequences disclosed by Haymore et al. are composed of two histidine residues, one histidine residue and one

aspartic acid residue. Nothing is mentioned about two histidine and two cysteine residues in combination.

Applicants remind the Examiner that to imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its character. *W.L. Gore Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983).

For the reasons expressed above, it is urged that the prior art references cited by the Examiner either singly or in combination fail to anticipate or suggest the present invention as defined by the amended claims. Accordingly, a *prima facie* case of obviousness has not been established by the Examiner, and the rejection under 35 USC § 103 should be withdrawn.

Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees to Deposit Account No. 11-0345. Please credit any excess fees to such account.

Respectfully submitted,
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MARKED UP VERSION OF AMENDED SPECIFICATION

Page 13, lines 30-32 should be deleted:

~~The use of an in vitro recombination technique for molecular evolution is described by Stemmer (Proc. Natl. Acad. Sci. USA, Vol. 91, 1994: 10747-10751).~~

MARKED UP VERSION OF AMENDED CLAIMS

Claims 1 and 3-5 should read as follows:

1.(currently amended) A peptide fragment having the general sequence

His-X^1-His-X^2-X^3-X^4-Cys-X^5-X^6-Cys,

where the variables X^1 to X^6 in the sequence have the following meanings:

X^1 = an amino acid selected from the group consisting of Ala, Val, Phe, Ser, Met, Trp, Tyr, Asn, Asp or Lys and the variables X^2 to X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^2 = an amino acid selected from the group consisting of Val, Ile, Phe, Pro, Trp, Tyr, Gln, Glu or Arg and the variables X^1, X^3 to X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^3 = an amino acid selected from the group consisting of Gly, Ile, Thr, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His and the variables X^1, X^2, X^4 to X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^4 = an amino acid selected from the group consisting of Val, Phe, Pro, Cys, Met, Trp, Asn, Glu, Arg or His and the variables X^1 to X^3, X^5, X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^5 = an amino acid selected from the group consisting of Gly, Ser, Cys, Met, Trp, Asn, Glu, Lys or Arg and the variables X^1 to X^4, X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^6 = an amino acid selected from the group consisting of Phe, Pro, Ser, Cys, Trp, Tyr or Gln and the variables X^1 to X^5 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His and

where at least one of the variabes X^1 to X^6 in the sequence is, independently of one another, Gln or Asn.

3.(currently amended) A peptide fragment as claimed in claim 1, in which the variables X^1 to X^6 in the sequence have the following meanings ~~independently of one another~~:

X^1 = an amino acid selected from the group consisting of Ala, Val, Phe, Ser, Met, Trp, Tyr, Asn, Asp or Lys;

X^2 = an amino acid selected from the group consisting of Val, Ile, Phe, Pro, Trp, Tyr, Gln, Glu or Arg;

X^3 = an amino acid selected from the group consisting of Gly, Ile, Thr, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg or His;

X^4 = an amino acid selected from the group consisting of Val, Phe, Pro, Cys, Met, Trp, Asn, Glu, Arg or His;

X^5 = an amino acid selected from the group consisting of Gly, Ser, Cys, Met, Trp, Asn, Glu, Lys or Arg;

X^6 = an amino acid selected from the group consisting of Phe, Pro, Ser, Cys, Trp, Tyr or Gln.

4.(currently amended) A peptide fragment as claimed in claim 1, in which the variables X^1 to X^6 in the sequence have the following meanings ~~independently of one another~~:

X^1 = an amino acid selected from the group consisting of Phe, Ser, Asn, Asp or Lys;

X^2 = an amino acid selected from the group consisting of Val, Ile, Phe, Pro, Gln, Glu or Arg;

X^3 = an amino acid selected from the group consisting of Gly, Ile, Thr, Met, Trp, Tyr, Asn, Asp, Glu, Arg or His;

X^4 = an amino acid selected from the group consisting of Val, Phe, Cys, Met, Trp, Asn, Arg or His;

X^5 = an amino acid selected from the group consisting of Gly, Ser, Cys, Met, Asn, Glu, Lys or Arg;

X^6 = an amino acid selected from the group consisting of Phe, Ser, Cys, or Tyr.

5.(currently amended) A peptide fragment as claimed in claim 1, in which the variables X^1 to X^6 in the sequence have the following meanings ~~independently of one another~~:

X^1 = Asn;

X^2 = Gln, Glu or Arg;

X^3 = Gly, Thr or Tyr;

X^4 = Asn or Arg;

X^5 = Gly or Lys;

X^6 = Cys.